

## CLAIMS:

1. A method of modulating endothelial cell activity, said method comprising modulating the functional activity of protein C $\zeta$  wherein up-regulating protein kinase C $\zeta$  activity to a functionally effective level up-regulates said cellular activity and down-regulating protein kinase C $\zeta$  activity to a functionally ineffective level down-regulates said cellular activity.
2. The method according to claim 1 wherein said endothelial cell is a vascular endothelial cell or a lymphatic endothelial cell.
3. The method according to claim 1 or 2 wherein said cellular activity is endothelial cell permeability.
4. The method according to claim 3 wherein said endothelial cell permeability is intercellular or intracellular.
5. The method according to claim 4 wherein said permeability is thrombin-induced vascular endothelial cell permeability.
6. The method according to any one of claims 1 to 5 wherein said modulation is up-regulation of protein kinase C $\zeta$  activity and said up-regulation is achieved by introducing into said endothelial cell a nucleic acid molecule encoding protein kinase C $\zeta$  or functional equivalent, derivative or homologue thereof or the protein kinase C $\zeta$  expression product or functional derivative, homologue, analogue, equivalent or mimetic thereof.
7. The method according to any one of claims 1 to 5 wherein said modulation is achieved by contacting said endothelial cell with a proteinaceous or non-proteinaceous molecule which modulates transcriptional and/or translational regulation of the protein kinase C $\zeta$  gene.

- 53 -

8. The method according to any one of claims 1 to 5 wherein said modulation is up-regulation of protein kinase C $\zeta$  activity and said up-regulation is achieved by contacting said endothelial cell with a proteinaceous or non-proteinaceous molecule which functions as an agonist of the protein kinase C $\zeta$  expression product.
9. The method according to any one of claims 1 to 5 wherein said modulation is down-regulation of protein kinase C $\zeta$  activity and said down-regulation is achieved by contacting said endothelial cell with a proteinaceous or non-proteinaceous molecule which functions as an antagonist to the protein kinase C $\zeta$  expression product.
10. The method according to claim 9 wherein said molecule is angiopoietin-1 or functional derivative, homologue, analogue, equivalent or mimetic thereof.
11. The method according to claim 9 wherein said molecule is chelerythrine chloride or bisindoylmaleimide I or functional derivative, homologue, analogue, equivalent or mimetic thereof.
12. The method according to claim 9 wherein said molecule is a mutant protein kinase C $\zeta$ , which mutant is characterised by substitution of the threonine residue at position 410 of the activation loop to alanine.
13. The method according to any one of claims 1 to 12 wherein said endothelial cell activity is modulated *in vivo*.
14. The method according to any one of claims 1 to 12 wherein said endothelial cell activity is modulated *in vitro*.
15. A method of regulating endothelial cell activity in a mammal, said method comprising modulating the functional activity of protein kinase C $\zeta$  in said mammal

- 54 -

wherein up-regulating protein kinase C $\zeta$  activity to a functionally effective level up-regulates said endothelial cell activity and down-regulating protein kinase C $\zeta$  activity to a functionally ineffective level down-regulates said endothelial cell activity.

16. The method according to claim 15 wherein said endothelial cell is a vascular endothelial cell or a lymphatic endothelial cell.
17. The method according to claim 15 or 16 wherein said cellular activity is endothelial cell permeability.
18. The method according to claim 17 wherein said endothelial cell permeability is intercellular or intracellular.
19. The method according to claim 18 wherein said permeability is thrombin-induced vascular endothelial cell permeability.
20. The method according to any one of claims 15 to 19 wherein said modulation is up-regulation of protein kinase C $\zeta$  activity and said up-regulation is achieved by introducing into said endothelial cell a nucleic acid molecule encoding protein kinase C $\zeta$  or functional equivalent, derivative or homologue thereof or the protein kinase C $\zeta$  expression product or functional derivative, homologue, analogue, equivalent or mimetic thereof.
21. The method according to any one of claims 15 to 19 wherein said modulation is achieved by contacting said endothelial cell with a proteinaceous or non-proteinaceous molecule which modulates transcriptional and/or translational regulation of the protein kinase C $\zeta$  gene.
22. The method according to any one of claims 15 to 19 wherein said modulation is up-regulation of protein kinase C $\zeta$  activity and said up-regulation is achieved by

- 55 -

contacting said endothelial cell with a proteinaceous or non-proteinaceous molecule which functions as an agonist of the protein kinase C $\zeta$  expression product.

23. The method according to any one of claims 15 to 19 wherein said modulation is down-regulation of protein kinase C $\zeta$  activity and said down-regulation is achieved by contacting said endothelial cell with a proteinaceous or non-proteinaceous molecule which functions as an antagonist to the protein kinase C $\zeta$  expression product.
24. The method according to claim 23 wherein said molecule is angiopoietin-1 or functional derivative, homologue, analogue, equivalent or mimetic thereof.
25. The method according to claim 23 wherein said molecule is chelerythrine chloride or bisindoylmaleimide I or functional derivative, homologue, analogue, equivalent or mimetic thereof.
26. The method according to claim 23 wherein said molecule is a mutant protein kinase C $\zeta$ , which mutant is characterised by substitution of the threonine residue at position 410 of the activation loop to alanine.
27. A method for the treatment and/or prophylaxis of a condition characterised by aberrant, unwanted or otherwise inappropriate endothelial cell activity in a mammal, said method comprising modulating the functional activity of protein kinase C $\zeta$  wherein up-regulating protein kinase C $\zeta$  activity to a functionally effective level up-regulates said endothelial cell activity and down-regulating protein kinase C $\zeta$  activity to a functionally ineffective level down-regulates said endothelial cell activity.
28. The method according to claim 25 wherein said endothelial cell is a vascular endothelial cell or lymphatic endothelial cell.

- 56 -

29. The method according to claim 25 or 26 wherein said cellular activity is endothelial cell permeability.
30. The method according to claim 29 wherein said endothelial cell permeability is intercellular or intracellular.
31. The method according to claim 30 wherein said permeability is thrombin-induced vascular endothelial cell permeability.
32. The method according to any one of claims 27 to 31 wherein said modulation is up-regulation of protein kinase C $\zeta$  activity and said up-regulation is achieved by introducing to said mammal a nucleic acid molecule encoding protein kinase C $\zeta$  or functional equivalent, derivative or homologue thereof or the protein kinase C $\zeta$  expression product or functional derivative, homologue, analogue, equivalent or mimetic thereof.
33. The method according to any one of claims 27 to 31 wherein said modulation is achieved by introducing to said mammal a proteinaceous or non-proteinaceous molecule which modulates transcriptional and/or translational regulation of the protein kinase C $\zeta$  gene.
34. The method according to any one of claims 27 to 31 wherein said modulation is up-regulation of protein kinase C $\zeta$  activity and said up-regulation is achieved by introducing to said mammal a proteinaceous or non-proteinaceous molecule which functions as an agonist of the protein kinase C $\zeta$  expression product.
35. The method according to any one of claims 27 to 31 wherein said modulation is down-regulation of protein kinase C $\zeta$  activity and said down-regulation is achieved by introducing to said mammal a proteinaceous or non-proteinaceous molecule which functions as an antagonist to the protein kinase C $\zeta$  expression product.

- 57 -

36. The method according to claim 35 wherein said molecule is angiopoietin-1 or functional derivative, homologue, analogue, equivalent or mimetic thereof.
37. The method according to claim 35 wherein said molecule is chelerythrine chloride or bisindoylmaleimide I or functional derivative, homologue, analogue, equivalent or mimetic thereof.
38. The method according to claim 35 wherein said molecule is a mutant protein kinase C $\zeta$ , which mutant is characterised by substitution of the threonine residue at position 410 of the activation loop to alanine.
39. The method according to claim 29, 30, 31, 33 or 35 to 38 wherein said condition is an inflammatory response.
40. The method according to claim 29, 30, 31, 33 or 35 to 38 wherein said condition is unwanted angiogenesis.
41. The method according to claim 40 wherein said condition is solid tumors, blood born tumors, tumor metastasis, benign tumors, rheumatoid arthritis, Crohn's disease, atherosclerosis, obesity, endometriosis, ocular angiogenic diseases, psoriasis, facial and truncal telangiectasias, or Osler-Webber Rendau syndrome.
42. Use of an agent capable of modulating the functionally effective level of protein kinase C $\zeta$  in the manufacture of a medicament for the regulation of endothelial cell activity in a mammal wherein up-regulating protein kinase C $\zeta$  activity to a functionally effective level up-regulates said endothelial cell activity and down-regulating protein kinase C $\zeta$  activity to a functional ineffective level down-regulates said endothelial cell activity.
43. Use according to claim 42 wherein said agent is a proteinaceous or non-proteinaceous molecule which modulates transcriptional and/or translational

- 58 -

regulation of the protein kinase C $\zeta$  gene, functions as an agonist of protein kinase C $\zeta$  activity or functions as an antagonist of protein kinase C $\zeta$  activity.

44. Use according to claim 43 wherein said antagonist is angiopoietin-1, chelerythrine chloride, bisindolmaleimide I or a mutant protein kinase C $\zeta$ , which mutant is characterised by substitution of the threonine residue at position 410 of the activation loop to alanine.
45. Use of protein kinase C $\zeta$  or a nucleic acid encoding protein kinase C $\zeta$  in the manufacture of a medicament for the regulation of endothelial cell activity wherein up-regulating protein kinase C $\zeta$  to a functional level up-regulates said endothelial cell activity.
46. Use according to any one of claims 42-45 wherein said endothelial cell is a vascular or lymphatic endothelial cell.
47. Use according to claim 46 wherein said endothelial cell activity is endothelial cell permeability.
48. A pharmaceutical composition comprising a modulatory agent and one or more pharmaceutically acceptable carriers and/or diluents.